Malaria vaccine

Towards an effective malaria vaccine

Pedro Aide, Quique Bassat, Pedro L Alonso

An effective malaria vaccine may be developed in the near future

When in 1955 the malariologist Paul Russell predicted without hesitation the imminent end of malaria,[1] little could he have imagined that half a century later malaria would still be one of the most important public health challenges in the world. At the beginning of the 21st century, 3000 million people (almost half the world's population) living in malaria endemic areas in 100 countries are at risk, with the biggest burden of both disease and death concentrated in African countries. Between 300 and 500 million clinical cases and up to 2.7 million deaths are believed to occur annually.[2 3]

Although there are four species of *Plasmodium* that infect humans, only two (*P vivax* and *P falciparum*) cause significant disease, with nearly all deaths being caused by *P falciparum*.

IS A MALARIA VACCINE NECESSARY?

Over the last century, malaria has disappeared from significant areas of the world, and in some places this has been due to the use of control measures. Nevertheless, in areas where this infection still occurs, we are witnessing an increase in the total number of malaria cases due to population growth, which implies that today more people die from this disease than 40 years ago.[4]

The causes of this resurgence are many. The parasite's extended and increasing resistance to the most common antimalarial drugs, the mosquito's resistance to the widely used insecticides, the hitherto insufficient interest of the pharmaceutical industry in developing new drugs, the shortcomings in the implementation of available control measures, the collapse of national malaria control programmes and the increase in tourism and the migration of non-immune populations to malaria endemic areas, have all contributed to the general rise in malaria cases.[5]

Despite the increasing availability of effective malaria control tools, which should have a combined positive effect on the dynamics of the pandemic, a better and definitive approach to deal with this disease is clearly needed. Vaccines, traditionally considered first-class public health tools, are relatively cheap, easy to administer and deployable through existing universal schemes. A malaria vaccine could therefore become the key element to boost malaria control.

WHY IS A MALARIA VACCINE NOT ALREADY AVAILABLE?

The development of a malaria vaccine is an old jigsaw puzzle which has not yet been solved and presents a formidable scientific challenge. Several factors may explain this historic failure to produce an effective vaccine.

From the immunological point of view, the parasite shows great complexity. The *Plasmodium* genus presents a myriad of antigens which vary throughout the different stages of its life cycle, and against which sequential consecutive immune responses are required. Moreover, many parasitic proteins exhibit high polymorphism, and a single parasitic clone may have up to 50 different copies of the gene coding for an essential protein, expressing a different version of such protein in each successive wave of parasitaemia. This particular antigenic variability appears critical for the parasite's survival, and clearly is a disadvantage not only for the infected individual but also for the scientists aiming to design a vaccine.

Our knowledge about the acquired immunity developed against the disease is limited and incomplete. So far, no surrogate of immunity has been found and there is no certainty about which specific antigens play a key role in the development of immunity.

Moreover, no appropriate animal model exists and the only way of testing the efficacy of a vaccine depends on logistically complex clinical trials being carried out in malaria endemic areas. The high calculated mean cost of developing a malaria candidate vaccine (around $500 million) and the length of the process before it can be marketed (up to 10–12 years),[6] has discouraged pharmaceutical companies from investing in vaccines destined for a market eager for solutions but too poor in resources to pay for them.

IS A MALARIA VACCINE FEASIBLE?

There are four lines of argument supporting the idea that malaria vaccines are feasible.

The first argument is based on the naturally acquired immunity that individuals living permanently in endemic areas develop. Partial immunity against the most severe forms of disease[7] (death and severe disease) is progressively acquired, followed by immunity against clinical episodes and finally suppression of the parasitaemia to low or undetectable levels.[8] Such protection requires a continued booster effect which, however, does not confer sterilising[9] immunity, as individuals may become infected although they do not develop clinical symptoms. If such a model could be reproduced by a vaccine, we would be able to confer solid protection against the disease.

The second model implies evidence of potential passive immunity against malaria. The administration of purified immunoglobulins from ''immune'' malaria patients has been shown to protect patients exposed to the infection.[10 11] Moreover, in endemic areas, newborn infants seem to be protected against clinical forms of the disease, a possible consequence of the passive transfer of maternal antimalarial antibodies during pregnancy.[12]

The third line of argument is supported by experiments carried in the 1970s, during which non-immune volunteers were intensively exposed to UV irradiation-weakened sporozoites. When the volunteers were re-challenged by normally infecting sporozoites, they had acquired, in up to 90% of cases,[13] complete (sterilising) although short-lived immunity. This supports the viability of a vaccine, and should be, despite obvious practical limitations, another model to imitate.[14] Recent research using genetically modified *Plasmodium* parasites (UIS3-deficient) has also shown that this model can be replicated successfully in rodents.[15]

Finally, several studies[16 17] have shown the efficacy of experimental malaria candidate vaccines in humans (adults and children). Nevertheless, despite different candidate vaccines successfully protecting individuals in clinical phase II trials and despite extensive immunological analysis, we still do not know on what immunological basis these individuals are protected, as no clear surrogate measures of immunity have been found.

STRATEGIES FOR VACCINE DESIGN

The ideal malaria vaccine would probably be one that was safe and induced sterilising life-long immunity against infection from childhood. However, this is unlikely in the short term. Given the lack of surrogate markers of protection and our incomplete understanding of

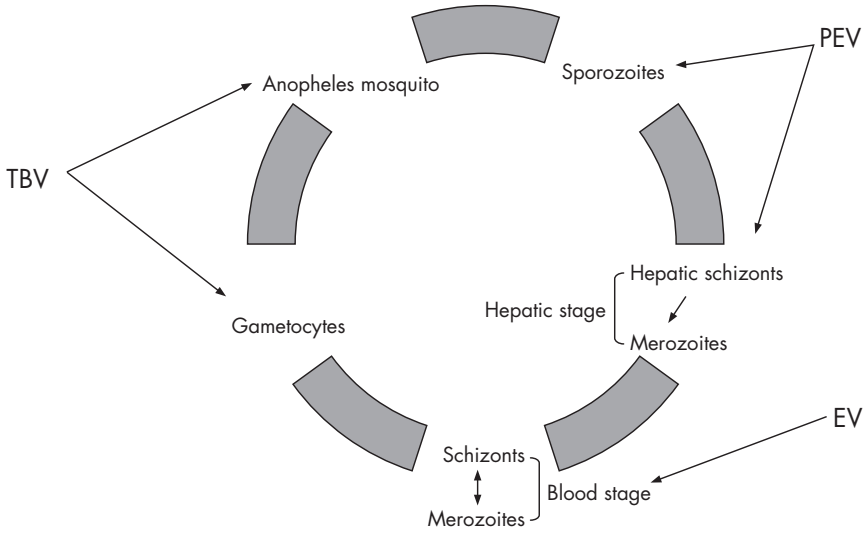

Figure 1 *Plasmodium* life cycle and theoretical activity points of the different malaria vaccines.

malaria immunity, the choice of adequate antigens becomes particularly difficult. It would be reasonable to suppose that antigens should be as conserved as possible, play a vital role in the parasite's life cycle and be amenable to immune challenge. Moreover, immune responses to that antigen should ideally correlate with a reduced risk of malaria. In the past, there has been a greater emphasis on trying to induce cellular responses together with antibody responses, particularly when targeting the pre-erythrocytic stages.[18–20]

The last few years have highlighted the key role that improved and more potent adjuvants may play. Identifying new powerful adjuvants that remain safe, effective and not too reactogenic will surely enhance the possibilities of the existing candidate antigens.

Malaria vaccines can be designed according to the target population or the life cycle stage targeted.

Vaccines designed according to the target population

Different vaccines are needed for different populations; a vaccine aimed at protecting children living in a malaria endemic area is not necessarily similar in its concept to a vaccine aimed at protecting non-immune individuals. In the first case, the vaccine does not need to be 100% effective, as its effect will add to the naturally acquired immunity. This vaccine would need to be directed against the asexual stages and imitate naturally acquired immunity. However, a vaccine aimed at protecting the non-immune individual (for instance, a tourist) requires 100% efficacy, as it would need to neutralise the parasite before it can reach the bloodstream and cause clinical symptoms. The model to follow in this case would be that of immunisation with irradiated sporozoites.

Vaccines designed according to the life cycle stage targeted

The complexity of the *Plasmodium's* life cycle suggests the possibility of establishing different antigenic targets for each stage. Figure 1 summarises the *Plasmodium* life cycle and the respective targets of the different types of stage-specific vaccines.

- Pre-erythrocytic vaccines (PEV) are directed against sporozoites or intrahepatic parasitic stages, and are designed to stop the parasite from reaching its erythrocytic stage so as to prevent any clinical manifestation.
- Blood stage or erythrocytic vaccines (EV) are directed against the blood stage antigens of the life cycle. They should therefore prevent the invasion of red blood cells by post-hepatic merozoites, speed the parasitised erythrocytes' clearance and therefore avoid their sequestration in the microvasculature. The vaccine would not interfere with infection but it would decrease the severity of symptoms.
- Transmission blocking or ''altruistic'' vaccines (TBV) would not benefit the individual but the community where vaccinated individuals live, by blocking human to human transmission. By targeting the parasite's sexual stages (using antigens expressed in the mosquito stages rather than in humans), this vaccine could prevent the appearance of mutant strains. Since the mosquito does not have an adaptive immune response, the *Plasmodium* genes coding for the mosquito-stage life cycle are remarkably conserved, and thus easier to identify and target.

The combination of a vaccine of this kind with a PEV or an EV could then avert the appearance of potentially dangerous immune selection.[21 22]

In reality, the predicted effects of such types of vaccines are generally wider than expected and may intertwine. Partially effective PEVs have shown protection against severe disease,[16] a characteristic traditionally believed to be typical of EVs.[23] It is believed that by decreasing the initial parasite inoculum, and subsequently causing a delay in the rupture of hepatic schizonts, a more benign illness may occur,[22] an identical mechanism to that proposed for bed nets.[24]

A possible strategy is to combine antigens from different stages (multistage vaccines) in order to trigger an intense and sequential immune response, or different antigens from the same phase (multivalent vaccines), so as to increase the efficacy and reduce the risk of emergent resistance. However, the inclusion of unnecessary components may increase both the cost and any undesired effects.

VACCINES IN CLINICAL TRIALS

The development of a malaria vaccine takes a long time and is expensive, and several phases must occur before a candidate vaccine can be tried in children.

Currently, several candidate vaccines are being developed, most of which are still in the preclinical phases. More than 50% of the approximately 75 candidate vaccines in active development today are based on just three antigens cloned two decades ago: the circumsporozoite protein (CSP), the merozoite surface protein (MSP) and the apical membrane antigen 1 (AMA-1).[18] The *Plasmodium falciparum* genome project has identified hundreds of parasite proteins that could form the basis for new vaccines.[25]

The most advanced candidate vaccine, the RTS,S/AS02A, has been developed and jointly financed by GlaxoSmithKline and the Malaria Vaccine Initiative (MVI).[26] This pre-erythrocytic subunit vaccine is based on the fusion of the surface antigen from the circumsporozoite (CS) with the hepatitis B surface antigen (HBsAg), formulated with the AS02A adjuvant. In a phase IIb clinical trial carried out in 2003 in children from 1 to 4 years of age in Mozambique, this vaccine was shown to be safe, immunogenic and efficacious, reducing *P falciparum* clinical malaria cases by 30% and episodes of severe disease by up to 58%.[16] Moreover, this efficacy did not seem to wane[22] after an 18 month follow-up period, when the protection was maintained.[27] These promising results need now to be confirmed in the ideal target population, which is children less than

Table 1 Major malaria candidate vaccines in clinical development[12 18 28]

Antigen	Name	Adjuvant	Clinical phase	Producer/group
Pre-erythrocytic (PEV)				
CSP	RTS,S[16 27 29]	AS02A	1a, 1b, 2a, 2b	MVI/GSK
CSP	RTS,S	AS01B	1a, 2a	WRAIR/GSK
CSP	RTS,S	AS01E	1a, 1b, 2a	MVI/GSK/WRAIR
Fowl pox 9 CSP+LSA-1 epitope/ MVA CSP+LSA-1 epitope		None	1a, 1b, 2a	Oxford
Fowl pox 9MVA polyprotein		None	1a, 2a	Oxford/EMVI
LSA-1 *E coli* expressed	LSA-NRC	AS02A	1a, 2a	GSK/WRAIR
LSA-1 *E coli* expressed	LSA-NRC	AS01B E	1a, 2a	GSK/WRAIR
Erythrocytic (EV)				
MSP-1 42 3D7 (FMP-1) *E coli* expressed	FMP1[30]		1a, 1b, 2a, 2b	WRAIR
MSP-1-C1 42	(FVO+ 3D7)	ALOH *P pastoris* expressed	1a	MVDU/NIH
MSP-1-C1 42	(FVO+ 3D7)	ALOH+CPG *P pastoris* expressed	1a	MVDU/NIH
AMA-1 3DT[31]	FMP2.1	AS02 *E coli* expressed	1a, 1b	WRAIR
AMA-1 C1	(FVO+ 3D7)	ALOH *E coli* expressed	1a, 1b	MVDU/NIH
AMA-1 C1	(FVO+ 3D7)	ALOH + CPG *E coli* expressed	1a	MVDU/NIH
AMA-1 C1	PfCP-2.9	ALOH/MontanideISA720/AS02 *P pastoris* expressed	1a	BPRC
SE 36	SERA	ALOH *E coli* expressed	1a	Osaka University, BIKEN Foundation
MSP3/GLURP	GMZ 2	ALOH *L lactis* expressed recombinant	1a	
MSP-1 19/AMA-1 chimera	PfCP2.9	*P pastoris* expressed	1a	SMMHS/Wanxing/MVI/WHO
Combination multi-stage vaccines				
Recombinant FMP-1 plus RTS,S, MSP-1 3DT+CSP			1a, 2a	WRAIR
Mimetopes delivered on virosome CSP, AMA-1			1a, 2a	Pevion
Transmission blocking vaccines (TBV)				
Pvs25 Saccharomyces expressed[32]		ALOH	1a	MVDU
Other approaches and targets				
PfEMP1	Malaria in pregnancy] vaccines[33		Pre-clinical	
Attenuated parasite (sporozoite)	Attenuated sporozoite vaccine[14 15]		Pre-clinical	Sanaria
GPI	Anti-toxic] vaccines[34		Pre-clinical	

ALOH, aluminium hydroxide; AMA, apical membrane antigen; CSP, circumsporozoite protein; EV, erythrocytic vaccines; GLURP, glutamate-rich protein; GPI, glycosylphosphatidylinositol; GSK, GlaxoSmithKline Biological; LAS, liver-stage antigen; MDVU, Malaria Vaccine Development Unit; MSP, merozoite surface protein; MVA, modified vaccine Ankara; NIH, National Institute of Health; PEV, pre-erythrocytic vaccines; WRAIR, Walter Reed Army Institute of Research.

1 year of age. Should this vaccine be similarly effective in this age group, the vaccine could be included in the Expanded Programme of Immunization (EPI), one of the few existing effective mechanisms for the universal distribution of health measures in poor countries.

Other candidate malaria vaccines in different stages of clinical development and further vaccine development strategies (including prime boost, virosomes, virus-like particles and peptides based on the important parasite antigens) are summarised in table 1. In the past 5 years, the number of groups working with malaria vaccines has grown from three to 11[21] and in the next few years we should have a clearer picture of the efficacy of these candidate vaccines.

CONCLUSIONS

The promising advances that the beginning of the 21st century is witnessing in the field of malaria vaccine research are framed in an atmosphere of optimism and research impetus that cannot and must not be wasted. Different private initiatives have worked together with the public sector in order to finance the research needed to obtain a vaccine that once seemed too far away. It is essential that this momentum is maintained to guarantee the development of an effective vaccine. We face the possibility of solving a formidable scientific challenge and must not undermine it. Vaccination of children from malaria endemic areas with an effective and safe vaccine, combined with the use of other proven effective control measures, could contribute decisively to decreasing the intolerable malaria toll. It may now be the appropriate moment to reflect upon the strategies that will be needed in the future to distribute this control tool at an affordable cost among those who need it most, an equal or even bigger challenge.[35]

Arch Dis Child 2007;**92**:476–479.
doi: 10.1136/adc.2005.092551

Authors' affiliations
Pedro Aide, National Institute of Health, Ministry of Health, Mozambique
Pedro Aide, Quique Bassat, Pedro L Alonso, Manhica Health Research Center, Maputo, Mozambique
Quique Bassat, Pedro L Alonso, Barcelona Center for International Health, Hospital Clinic, University of Barcelona, Barcelona, Spain

Correspondence to: Pedro L Alonso, Centre de Salut Internacional, Hospital Clínic de Barcelona, Villarroel 170, 08036 Barcelona, Spain; palonso@clinic.ub.es

Accepted 7 February 2007

Competing interests: None.

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Adoption

Intercountry adoption

Mary Mather

More research is needed on the long-term outcomes of children adopted from other countries

Celebrity adoption was one of the media sensations of 2006, the year every British newspaper suddenly had an opinion about intercountry adoption. What some praised as the altruistic rescue of a child from poverty and early death, others criticised as an adult-driven, largely commercial transaction. Few editorials considered the consequences for the child growing up in a ''rainbow family'' far from home or the plight of those children for whom rescue was not an option.

Unlike newspaper editors, paediatricians instinctively support policies that are in the best interests of children. However, forming an opinion about intercountry adoption can be an ethical minefield. While adopters are often driven by humanitarian motives, the children they crave are potentially very saleable items in unscrupulous hands. Few would wish to insult the good intentions of adoptive parents. However, it would be naive to deny that corruption and criminality can exploit the desperation of parents caring for children they can ill afford and the yearnings of those with none.

In a perfect world without war and gross inequities in living conditions, intercountry adoption would not exist. To leave the country of one's birth and culture is to undertake an uncertain and hazardous journey which, given a free choice, few would attempt. For a child, this is also a risky and disempowering process. The decision to move is normally made for a child rather than by the child. Children move from the familiar to the different and from fitting in to standing out. While the change is often from poverty to relative wealth, wealth alone cannot guarantee a better life.

THE DEMOGRAPHICS OF INTERCOUNTRY ADOPTION

Intercountry adoption started in North America primarily as a philanthropic response to the devastation following World War II and initially involved children moving from orphanages in Europe to North America.[1] As a more global phenomenon, it has grown rapidly since 1990 when the world first discovered Romanian orphans. In affluent societies, increasing demands for children, particularly babies, coupled with a marked decrease in domestic adoption has fuelled this growth. The internet has also increased public awareness about the availability and unmet needs of children in developing nations from where the vast majority of adoptions now originate.

Although accurate, up-to-date statistics are extremely difficult to obtain, intercountry adoption probably represents the